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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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LI & ALTER
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MIAMI, FL 33176

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/253,573	CHEN, HAI XING	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *06 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,6-8,11,12 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,6-8,11,12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *19 February 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 11/6/03.

Applicant listed as pending claims 1, 2, 6-8, 11, 12, and 14 and 30-43 as pending. This is incorrect. Claims 30-43 were canceled as requested by Applicant in the amendment filed 11/15/02. Claims 1, 2, 6-8, 11, 12, and 14 remain pending and are under consideration in this Office Action.

Rejections Withdrawn

Applicant's amendments were sufficent to overcome the reejctions for new matter and lack of adequate written description set forth in the previous action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1, 2, 6-8, 11, 12, and 14 stand rejected under 35 U.S.C. 1 12, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is a method for producing and delivering protein in vivo. The method requires collecting from a mammal progenitor cells of red blood cells,

transfecting these cells with an expression construct comprising a globin promoter which is active only in progenitor cells of red blood cells, operably linked to a gene encoding a protein heterologous to red blood cells, and reintroducing the transfected cells into the mammal. The protein is subsequently expressed such that it is contained only in red blood cells. The protein is delivered into the blood stream by lysis of the red blood cells. The claims require that the expressed protein must be contained only in red blood cells and not in any other type of cell.

It was recognized in the art at the time of the invention that the process of introducing a transgene into cells with multipotential developmental capacity and confining transgene expression to one secondary lineage is unpredictable. Rivella et al (Seminars in Hematology 3542): 1 12-125 (1998)) discussed this topic in the context of delivering beta globin genes to hematopoietic stem cells for production of globins in red blood cells. Genetic alteration of HSC to alter their progeny requires use of a vector that stably integrates in chromosomal DNA, or remains as a stable episome or additional chromosome. Most non-replicating episomal vectors are lost during clonal expansion, thus adenovirus and herpes virus vectors, embraced by the instant claims, are not suitable for long term modifications of hematopoietic tissue such as would be required for the therapeutic applications envisioned throughout the instant specification (discussed more thoroughly below). See page 113, column 1, lines 4-10, and lines 3-12 of paragraph bridging columns 1 and 2 of Rivella. At the time of the invention, the state of the art of non-viral systems was less advanced than that of viral systems and was less efficient due to poorer entry into primary cells, lysosomal degradation after entry,

poorer transport to the nucleus and less frequent chromosomal integration. As such, integrating viral vectors are currently the vectors of choice for delivering genes to HSCS for expression of genes in red blood cell precursors. See page 114, column 1, lines 13-21 of first full paragraph; and second full paragraph. At the time of the invention, retroviral vectors were the integrating viral vectors of choice for gene delivery to HSCS because they generally can accommodate larger transgenes and are much better characterized than alternatives such as adeno-associated virus and SV-40 based vectors. See paragraph bridging pages 113 and 114. However, retroviral vectors frequently suffer a silencing of expression. For example, Verma (1998) teaches that mouse cells comprising retroviral constructs designed to express factor IX suffered a silencing of expression within 5-7 days of reintroduction into a mouse. See page 240, column 2, lines 4-17. Verma indicates that it is possible to overcome this problem in some cases by finding the appropriate enhancer/promoter combination, but states that "the search for such combinations is a case of trial and error for a given type of cell." See sentence bridging columns 2 and 3 on page 240. Even more pertinent to the instant invention, Verma notes that there is "a lack of good enhancer-promoter combinations that allow sustained production of high levels of protein in" hematopoietic cells. See page 240, column 3, lines 16-24.

In practice, the use of retroviral vectors to transfer genes to precursors of red blood cells and to subsequently obtain expression has been unpredictable. For example, Hoogerbrugge et al (Gene Therapy (1996) 3: 179-183) used retroviral vectors to transfer the adenosine deaminase (ADA) gene to CD34+ marrow cells isolated from

patients, and subsequently reimplanted the cells back into the patients. No expression of the ADA gene was detected in patients, due likely to poor efficiency of gene transfer to target cells. See abstract. Similarly Dunbar et al (Human Gene Therapy (1998) 9: 2629-2640) used retroviral vectors to transfer the glucocerebrosidase (GC) gene to CD34+ cells isolated from patients, and subsequently reimplanted the cells back into the patients. No expression of the transduced GC gene was detected in patients. See abstract and paragraph bridging columns 1 and 2 on page 2635. Dunbar suggested that for therapeutic results to be obtained cell marking efficiency should be improved by two orders of magnitude, and that this would require development of improved methods of gene transfer and engraftment. See paragraph bridging columns 1 and 2 on page 2638.

Further evidence that the transfer of genes to precursors of red blood cells is unpredictable comes from Orlic et al (Blood (1998) 91(%: 3247- 3254). Orlic teaches that there are examples gene transfer to mouse HSCS, and subsequent therapeutic effects, however, this appears to be due to the high efficiency of infection of mouse HSCS by retroviral vectors. Orlic teaches that this efficiency is not observed in other models, noting that fewer than 1% of circulating blood cells contained delivered genes in Rhesus monkey and human experiments. See abstract and last sentence of second paragraph, column 1, page 3247. Thus the art at the time of the invention did not teach how to obtain efficient transfer of genes to red blood cell precursors such that the gene products were predictably expressed organisms other than mice.

The claimed invention faces the further problem of directing expression not only into precursors of red blood cells, but restricting expression such that it occurs only

those precursors that are committed to a red blood cell fate. That is, the claims require that no cell other than a red blood cell may contain the gene product encoded by the expression construct. This is to be accomplished through the use of promoters which are "active only in progenitor cells of red blood cells". By way of exemplification, the specification discloses a "hemoglobin promoter". See e.g. page 8, line 11. The phrase "hemoglobin promoter" is a term of art referring only to certain plant promoters. See e.g. Paper No. 21, paragraph bridging pages 15 and 16. For the purpose of this rejection, the Office understands "hemoglobin promoter" to mean a globin promoter. The prior art teaches that control of globin gene expression is very complex and depends on a 21 kb locus control region (LCR) comprising a smaller core region referred to as a micro LCR which is required for erythroid specific expression. However, the LCR is subject to position effects when inserted into heterologous chromosomal regions, and expression decreases over time in vivo. See for example Rivella et al, abstract. Further, there is evidence that the combination of an LCR and a globin promoter is not sufficient to limit expression to red blood cell precursors. For example, Teitz et al (DNA and Cell Biol. (July 1994) 1347): 705-710) attempted to model hematopoietic neoplasia by making transgenic mice in which expression of the SV40 large T antigen was placed under control of the globin micro LCR and beta globin promoter. However, instead of developing hematopoietic neoplasia, the mice developed soft-tissue sarcomas, and pancreatic islet cell tumors. This is clear evidence that the expression of a gene under the control of a globin promoter was not restricted to progenitor cells of red blood cells.

It is noted that there are numerous reports of erythroid-specific expression of globin transgenes under the control of the globin micro LCR and a globin promoter (summarized in Tewari et al (Dev. 122: 3991-3999 (1996), see page 3991, paragraph bridging columns 1 and 2) . However it is unclear, particularly in view of the results of Teitz et al, whether or not erythroid specific expression of non-globin genes can be predictably obtained through linkage to globin promoters. Tewari (1996) used transgenic mice to study the requirements for erythroid specific activity of the micro LCR by linking it, or its fragments, to an Hsp-68 promoter driving expression of a reporter gene. Only constructs comprising the entire micro LCR, or a fragment referred to as 5'HS3, could drive expression in erythroid cells, and this expression occurred only in embryonic stages of development. See page 3992, column 1, lines 19-26. Neither the prior art of record nor the instant specification provides guidance as to what specific sequences are required in order to predictably provide the promoter activity required by the instant claims, i.e. activity only in progenitors of red blood cells that are committed to a red blood cell fate. Thus one of skill in the art would have to discover these sequences before practicing the scope of the invention involving promoters other than globin promoters. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk MS, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of promoters that are active only in progenitor cells of red blood cells committed to a red blood cell fate when linked to heterologous genes and inserted into heterologous chromosomal, viral, or plasmid contexts is not an inconsequential detail which can be omitted in the process of providing an enabling disclosure. Rather this is a critical element required for the practice of the invention as claimed. Because the specification fails disclose any example of such a promoter, there is a failure to meet the enablement requirement.

It is noted that the scope of cells embrace by the instant claims is not limited strictly to HSCS and their descendants in the pathway of erythrocyte differentiation. The claims also embrace any cell that can be construed as a progenitor of a red blood cell, including embryonic stem (ES) cells which ultimately give rise to all types of cells in an organism. The specification fails to teach how to deliver a vector to an embryonic stem cell so that it is maintained throughout differentiation and such that appropriate expression and deposition of the desired protein in red blood cells occurs. As discussed above, in order for red blood cell precursors to inherit an expression construct from embryonic stem cells, the construct would have to be integrated into the genome. The

prior art teaches two ways to do this. One is by including within the expression construct a selectable marker, transfecting ES cells, selecting for the marker, and transplanting the ES cells into a host, e.g. a blastocyst. At the time the invention was filed, this approach had been shown to work only in mice, due to the fact that embryonic stem cells from other organisms lost the ability to differentiate during the selection procedure. The state of the art with respect to the use of ES cells from non-mouse organisms is set forth by Bradley (1992), Seamark (1994), and Mullins (1996). Bradley et al (1992) taught that there were no ES cells for any animal other than a mouse which had been established to give rise to somatic tissues or germ cells in vivo. Seamark (1994) disclosed that totipotency for ES cell technology in many species had not been demonstrated prior to the time of filing (page 654 column 2, paragraph 3, Abstract). Mullins taught that techniques for the use of non-mouse ES cells are based on those developed for mouse ES cells, and that these techniques are in need of further refinement (pages 37 and 38). Specifically, chimeric non-mouse animals have been created by the injection into blastocysts of freshly isolated ES cells, and totipotency of these cells has been demonstrated. However, attempts to culture non-mouse ES cells result loss of totipotency. ES cells must be cultured in order to select for the integration events that would be required to practice the instant invention. The specification has failed to teach how to obtain such integration events in ES cells while maintaining their ability to differentiate into red blood cells. Another way to integrate an expression construct into the genome of an ES cells is through the use of an integrating viral vector,

e.g. a retrovirus.. However, as discussed above, the prior art teaches that the use of retroviral vectors is problematic because of gene silencing and position effects.

Having addressed the scope of cells, vectors, and promoters required to make the invention, the issue of how to use the invention will now be considered. The asserted use of the invention is the delivery of therapeutic proteins. See page 10, lines 13-15, page 11, lines 10-20, page 13, lines 7-24, and page 14, line 4 to page 16, line 1. The specification discloses that the claimed invention "has a broad scope of applications in treating diseases". See page 14, lines 4 and 5. Specific diseases which may be treated using the claimed invention including cystic fibrosis, Duchenne muscular dystrophy, hemophilia A, Huntington's disease, familial hypercholesterolemia, Fragile-x syndrome, and cancer in general. See page 14, lines 12-15 and paragraph bridging pages 14 and 15. The specification also considers treating diseases in general through the delivery of enzymes and hormones. See page 14, lines 15-30. The specification asserts no use for producing and delivering protein in vivo other than for the treatment of disease. For these reasons, in order to enable the invention for its intended use, the specification must teach how to use the invention for the treatment of the range of diseases set forth in the specification.

A review of the prior art shows that techniques for isolating, transfecting and successfully engrafting red blood cell precursors were established at the time of the invention. See US Patent 5,665,350, e.g. claims 2 and 4-6. It is also clear that this technique could be used to produce the encoded proteins. See e.g. Plavec et al (Blood 81(5):1384-1392, 3/1993), abstract. However, obtaining sufficient expression of proteins

for therapeutic purposes is problematic. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). The instant specification acknowledges the unpredictability of the art at page 1, lines 1 1-19, which indicates that "no approach has definitively improved the health of one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide."

The specification teaches the use of a hemoglobin promoter to drive expression of therapeutic genes. Rivella (1998) set forth the state of the art at the time of the invention with regard to gene therapy based on delivery of globin promoter-driven constructs to HSCS. After the time of filing Persons et al (Proc. Nat Acad. Sci. USA 97(10):5022-5024, 5/2000) reviewed the history of attempted therapy of hemoglobin disorders by ex vivo transfection and reimplantation of red blood cell precursors. Persons emphasizes the difficulty in obtaining globin promoter-driven expression of proteins in red blood cell precursors, specifically citing problems with gene silencing and position effect variegation. See entire document , especially paragraph bridging columns 1 and 2 on page 5022; column 2, line 21 through first full paragraph in column 3, page 5022. Rivella states the same concerns regarding position effects and silencing (see abstract, and paragraph bridging columns 1 and 2 on page 121), and notes that the procedures for expansion and transduction of human HSC at the time of the invention were inadequate for gene therapy (see page 1 13, column 1, last sentence of first full paragraph). Thus prior to, and subsequent to, the time the invention was filed, those of skill in the art were unable to obtain therapeutic concentrations of proteins within red blood cells using globin promoters. The claimed invention requires delivery of proteins after lysis of red blood cells in the spleen, thus the problem of poor expression of protein is compounded by the problem of dilution into the spleen and blood stream. This necessarily lowers the concentration of the proteins and points to a need for far higher efficiency of expression than that obtained using globin promoters because the specification fails to teach any method of targeting proteins to any specific tissue. The

claimed mode of delivery also fails to account for the biology of some of the disorders it is intended to treat. For example, the specification teaches treatment of cystic fibrosis by supply of a desired protein. See page 14, lines 4-15. Cystic fibrosis is caused by a defective version of a transmembrane ion transporter, the cystic fibrosis transmembrane conductance regulator (CFTR), and the effect of the disease is manifested in the lungs. Certainly one could not expect to deliver a functional CFTR and expect it to spontaneously integrate into the appropriate alveolar membrane without the aid of a ribosome and from the extracellular side of the membrane. However, the specification provides no guidance or examples as to how one of skill in the art could treat this loss of function by delivery through the blood of any desired protein.

The specification fails to identify specific proteins which should be used to treat a variety of the diseases which are asserted to be treatable with the instant invention, such as Huntington's disease, Gaucher's disease, familial hypercholesterolemia, and cystic fibrosis. Furthermore the specification fails to give any guidance whatsoever as to how much of any specific gene product would be required to treat any given disease, or how to obtain any specific dosage or administration profile. It fails to teach how many cells should be delivered for any given treatment or how to protect released proteins from proteases present in the blood.

In summary, the prior art shows that the process of delivering genes to red blood cell precursors such that their expression is restricted to cells committed to a red blood cell fate was highly unpredictable at the time of the invention due to a variety of factors including poor transduction of red blood cell precursors, poor expression of delivered

genes, uncertainty as to what promoter sequences can restrict expression to cells committed to a red blood cell fate, and silencing of viral vectors and globin-promoter driven expression constructs. Similarly, the prior art taught that the only asserted use of the claimed invention, gene therapy, generally lacked enablement at the time of the invention due to poor delivery and expression of therapeutic genes. More particularly, prior to and after the time of filing those of skill in the art found that the available methods for delivery of genes to HSCS and expression of genes in cells committed to a red blood cell fate were inadequate for purposes of therapy. Because the prior art lacked the guidance and teachings to allow one of skill in the art to practice the invention as claimed, the specification must fill this void in order to enable the invention. However, the specification adds nothing to the teachings of the prior art with respect to identifying new target cells for transduction, improving transduction efficiency of known target cells, improving gene expression in transduced cells, overcoming the problems of position effects and gene silencing, or identifying promoter sequences that limit expression to cells committed to a red blood cell fate. Because the specification fails to provide that which was missing from the prior art, and which is critical to the practice of the claimed invention, it fails to adequately enable the claimed invention.

Response to Arguments

Applicant's arguments filed 11/6/03 have been fully considered as they apply to the enablement rejection above but they are not persuasive. The arguments extend from page 7 to page 17 of the response.

At page 7 Applicant expresses surprise at the withdrawal of finality in the previous Office Action. Withdrawal of finality was necessariy in order to more clearly and completely set forth the relevant issues in prosecution, e.g. the issue of new matter, and the issues of the scope of cells, vectors, and promoters required to make the invention.

At page 8 Applicant establishes the position that the claimed invention is a method of in vivo protein production and delivery, asserting that although the invention may be used for disease treatment, it is not intended to be a specific gene therapy protocol. This raises the question of for what, other than gene therapy, the invention is intended to be used. The Examiner has carefully read the specification and found that, as stated in the rejection above, the specification asserts no use for the production and delivery of proteins in vivo other than therapy. Throughout the length of prosecution, Applicant has yet to point to any passage in the specification that asserts any use for the in vivo delivery of proteins other than therapy.

Applicant states at page 9 that the Examiner has failed to point out any particular claim elements which are broader than the scope of producing a protein only in the progenitor cells of red blood cells, and delivering the produced protein into the blood stream by rupture of the red blood cells. Applicant further argues that the Examiner has failed to point out any inconsistency in the plain meaning of the claim terms to indicate that the claim terms are broader than a method of producing a protein only in the progenitor cells of red blood cells, and delivering the produced protein into the blood stream by rupture of the red blood cells. The essence of Applicant's argument

is that rejection is applied to an invention that is not within the scope of the claims. This is unpersuasive because the claims cannot be considered in a vacuum and must be read in light of the specification. The scope intended to be embraced by the claims is determined by reading the claims in light of the specification. It is abundantly clear from a reading of the specification that the claimed invention is meant to be used for therapeutic purposes. As noted above, the specification asserts no use for producing and delivering protein in vivo other than for the treatment of disease. So, in order to enable the invention for its intended use, the specification must teach how to use the invention for the treatment of the range of diseases set forth in the specification.

Applicant argues at page 10 that it is well settled that the specification need not enable all possible embodiments. This is true, however, Applicant has failed to point to a single embodiment asserted in the specification other than therapy. Assertions that embodiments such as those discussed at page 14, and including non-tissue specific methods for the synthesis of proteins; means to control the expression and production of proteins in the precursors of red blood cells; taking advantage of the lack of a nucleus in a red blood cell to provide enhanced stability of proteins after their production; bypassing exocytosis and secretion pathways for protein release; and using a hemoglobin promoter to control expression of proteins in red blood cell precursors, are not utilities per se but rather research objectives that must be achieved in order to generate a therapeutically relevant expression level of any exogenous protein in only altered red blood cells in any mammal. As such, and not withstanding the lack of reasonable predictability in utilizing any contemplated in vivo altered red blood cell as a

bioreactor to produce therapeutically relevant amounts of any exogenous protein in any mammal having a protein deficient related disease or disorder, it is not apparent to one of skill in the art how any of these research utilities can be reasonably and predictably practiced within the context of the Wands factors, particularly given the doubts expressed in the art of record and the reasons set forth in the stated rejection. For this reasons, Applicant's arguments that the Examiner has improperly focused on gene therapy are unpersuasive. Furthermore, the enablement rejection considers the scope of cells, vectors, and promoters not only within the context of therapeutic applications, but within the broader context of merely expressing proteins in vivo. Applicant has presented no evidence or argument to show that the specification, or teachings in the art, overcome the art-recognized concerns relating to vector and promoter silencing discussed in the rejection. Clearly these concerns apply to the entire scope of expressing proteins in vivo, regardless of the intended purpose of expression. So, even if the enablement of gene therapy was not an issue for consideration here, use of the globin promoter as required by the claims is unpredictable in view of the teachings of e.g. Persons and Rivella, discussed above with regard to silinceing and position effects.

At pages 11 and 12 Applicant addresses the Teitz references previously cited in the enablement rejection. Teitz (1994) was relied upon in the determination of whether or not the specification taught how to make an expression construct with a promoter that was active only in the progenitor cells of red blood cells. Teitz (1994) teaches that expression constructs comprising the beta globin promoter and LCR linked to the SV40

T antigen coding sequence were expressed in non-erythroid tissues, i.e. sarcomas and pancreatic islet tumors. Teitz (1995) shows that a beta globin LCR linked to a T antigen promoter also leads to expression in non-erythroid cells. See paragraph bridging columns 1 and 2 on page 309. Applicant argues that the Teitz references provide no clear evidence that expression of a gene under control of a globin promoter would not be restricted to erythroid cells. Applicant's attention is directed to Teitz (1994) which provides objective evidence that the beta globin promoter and LCR do not limit expression solely to the progenitor cells of red blood cells as required by the claims, but rather allow expression in pancreatic islet tumors and sarcomas. As noted by Applicant, Teitz explains the sarcoma observation by speculating that the LCR/beta globin promoter is active in muscle cells due to binding of muscle specific transcription factors. As an alternative explanation applicant relies on statements from Teitz (1995) regarding the activity of a different promoter construct (LCR/T antigen promoter) in different cells (thymoma cells). Applicant has presented no reason why this explanation of the activity of a different promoter construct in different cells should be substituted for the explanation given by Teitz for the activity of the LCR/beta globin promoter construct in sarcoma cells, and has presented no evidence to indicate that this explanation is more likely. In other words, the simplest explanation for the expression of the T antigen in sarcoma cells is the activity of the promoter to which the T antigen gene was operably linked, i.e. the LCR/beta globin promoter. Applicant has provided no evidence that there is a more likely explanation than this. As such, even if the specification were

enabling for delivery of proteins in vivo, it would not be enabling for the scope of a "promoter that is active only in progenitor cells of red blood cells".

Applicant appears to attempt to support the position that the results of Teitz do not provide objective evidence for activity of the beta globin promoter in cells other than erythroid precursors by reference to a report in New Scientist published in October of 2002, after the instant Application was filed. If the Examiner understands Applicant correctly, Applicant relies on this reference to show that gene therapy expression constructs can cause leukemia if they integrate close enough to an oncogene to result in activation of the oncogene by the expression construct's promoter. It is unclear how this is intended to support Applicant's position. The data of Teitz (1994) clearly demonstrate that the T antigen was expressed in the cells in question, and Applicant has produced no evidence to suggest that it was not. Perhaps Applicant intended to suggest that this expression is due to integration of Teitz's expression vector near a strong chromosomal promoter active in muscle cells, such that the T antigen was expressed due to this promoter? If so, Applicant has presented no evidence that this has occurred, nor any reason to favor this explanation over that of Teitz. For these reasons Applicant's arguments regarding Teitz are unpersuasive.

At pages 12 and 13 of the response Applicant argues that in vivo protein delivery and expression are enabled as evidenced by the Hollis reference (US Patent 5,538,885). This argument is unpersuasive because Hollis was granted claims to composition, i.e. an expression system, and a method of using the system to produce a protein. Clearly, and in contrast to the instant claims, the invention of Hollis could be

used in vitro, and is enabled to that extent. To the extent that the method of Hollis might be used in vivo, Hollis teaches the utility of producing recombinant proteins for a purpose other than gene therapy, i.e. purification. See column 8, lines 18-24. The instant specification recites no such use, and the instant claims require "delivering a protein in vivo". This is clearly distinct from the asserted use of Hollis limited to production of the recombinant protein for non-therapeutic use, i.e. purification.

Applicant further argues at page 13 that it would be unjust to require applicant to delay seeking patent protection on a mechanism of protein delivery until after "a specific gene therapy has been discovered and has proven clinical use." This is unpersuasive for the reasons set forth above, i.e. enablement of the claims depends on whether the specification teaches how to make and use the invention. In this case the only asserted use of the invention is in gene therapy. For this reason, the specification must enable the use of the invention in gene therapy. The specification fails to do this for the reasons given above.

At page 14 Applicant asserts that the claimed invention may be viewed as a process which produces a product (gene therapy), and argues that the process is separate from the product. In support of this position Applicant draws an analogy to a method of producing time-release capsules for vitamin C, arguing that they would not be responsible for the clinical use of vitamin C. This is unpersuasive for two reasons. First Applicant's logic regarding enablement and the relationship between a product and a process of using it is flawed. If the use of a product is not enabled, then a method for

making that product is cannot be enabled unless it can be used to make some other useful product. Second, the analogy is improper because one of skill in the art can clearly use vitamin C, therefore a method of delivering it in vivo can be enabled. In the instant case, the specification fails to teach how to produce and deliver proteins for the intended therapeutic purpose.

Similarly, Applicant argues at page 15 that if a valve is used in an instrument does not mean that a claim of a new method of making the valve must be accompanied by an enabling disclosure of how to make the instrument. This is unpersuasive because, it is not necessarily true. If the only disclosed use of the valve is its use in the instrument, and there is no other readily apparent use for the valve, then neither the valve nor the method of making it is enabled unless the instrument is enabled.

At pages 15-17 Applicant asserts that the claimed rejection has a utility beyond gene therapy, i.e. the invention could be used to produce protein for the purpose of purification. In Applicant's explanation, the blood stream of the mammal of the invention is thought of as a bioreactor. To support this argument Applicant notes that mammals have been used in the past as bioreactors, specifically citing the use of mammary gland expression and secretion of proteins into milk. This argument is unpersuasive because it is based on non-analogous art. Production of a protein in transgenic mammary gland tissue is not the same as production in a small number of hematopoietic cells and release into the blood stream. The transgenic animals used as bioreactors in these applications contain a copy of the transgene in every cell, and every mammary gland cell in the animals is capable of expressing the protein. In stark contrast, the instant

application requires the isolation of a quantity of red blood cell precursors from a mammal, genetic modification of the cells, and reimplantation of the cells. Applicant has presented no evidence that one could hope to approach the efficiency of expression obtained in the mammary bioreactor model, thus it is not at all clear that one of skill in the art would find it readily apparent that the invention could be used for this purpose without further modification.

For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-

272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.